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EXAMINER
GANGLE, BRIAN J

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,753	PIZZA, MARIAGRAZIA	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-19,22-26 and 28* is/are pending in the application.

4a) Of the above claim(s) *15-19,22-25 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-14 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and remarks, filed on 3/28/2008, are acknowledged. Claims 4-19, 22-26, and 28 are pending. Claims 4-5, 8-14, 16-19, 26, and 28 are amended.

Election/Restrictions

Applicant requests that claims 16-19 and 22-25 be examined, as they are dependent on claim 4, "which is the elected invention of Group II." Applicant is reminded that these claims, while they are dependent on claim 4, are still drawn to different inventions than Group II as set forth in the restriction requirement.

Claims 15-19, 22-25, and 28 are withdrawn as being drawn to nonelected inventions. Claims 4-14 and 26 are currently under examination.

Specification

The objection to the specification for use of the trademark TWEEN is withdrawn in light of applicant's amendment thereto.

Claim Rejections Withdrawn

The rejection of claims 5, 7, 9, 11, and 13 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "identity," is withdrawn in light of applicant's amendment thereto.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 4-14 and 26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained for the reasons set forth in the previous office action.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. That "the examiner has not provided any reason to doubt that the specification fails to provide an adequate written description of the claimed invention."

2. That the five proteins in the composition are known and they have been described in the specification. Applicant asserts that NadA has been described showing alignments that highlight conserved regions, and variants and fragments have been explored. Applicant further asserts that many variants of NMB1870 have been disclosed, including more than 20 sequences.

3. That, with regard to claim 4, the designations NadA, 741, 936, 953, and 287 do not render the claims indefinite simply because they are laboratory designations. Applicant argues that "one of skill in the art is deemed to read claims in light of the art and in light of the specification." Applicant asserts that "in the case where a designation is not art recognized, one of skill in the art could readily refer to the specification and have no confusion as to the metes and bounds of the claimed invention given that there is a clear correspondence between the claimed designations and the art recognized designations." Applicant has replaced the designations 741, 936, 953, and 287, with the designations NMB1870, NMB2091, NMB1030, and NMB2132, and contends that these designations overcome the rejection because these are art recognized designators that were published by Tettelin.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, applicant is correct. As set forth previously, the specification fails to provide adequate written description for the claimed invention. The examiner has not provided any reason to doubt this. In the previous office action, the examiner clearly set forth legal and scientific reasoning to show a lack of written description. This reasoning is restated below.

Regarding argument 2, applicant is correct that the proteins in the claimed composition are known proteins. Several sequences for some of these proteins are known. However, applicant has not simply claimed a composition comprising these proteins and variants thereof. The claimed composition must induce a bactericidal antibody response against particular strains

of *Neisseria meningitidis*. As taught in basic immunology texts, an epitope or antigenic determinant interacts with its corresponding antibody based on the three-dimensional structure of both molecules and the fit between them (Cruse *et al.*, Illustrated Dict. of Immunology, 2nd ed., CRC Press, 2003, page 46). These epitopes can be conformational (or discontinuous) epitopes which are formed from separate regions in the primary sequence that are brought together by proper protein folding. Antibodies which bind to conformational epitopes will only bind to proteins folded into their proper native state (Cruse *et al.*, page 166). There are also linear epitopes, which are regions of six amino acids in the primary sequence of a protein. These are generally not found on the surface of a folded protein and are only available to antibodies upon denaturation of a protein (Cruse *et al.*, page 382). Since the instant claims involve methods of inducing an immune response specific for an organism, not antibodies specific for a particular linear protein, said antibodies must bind to a protein that is in the proper folded state and which is found on the surface of the organism, and therefore must bind to a conformational epitope. Since a conformational epitope is only found in a properly folded protein and can contain discontinuous portions of the protein, there is no way that one could determine whether a given polypeptide would bind to the antibody unless this were empirically tested. Any change (including deletions and substitutions), anywhere along the polypeptide is likely to alter the three-dimensional structure and folding of the protein, thus altering the antibody-antigen interaction. This is further supported by other authors such as McGuinness *et al.* (Mol. Microbiol., 7:505-514, 1993) and Moudallal *et al.* (EMBO Journal, 1:1005-1010, 1982), who have shown that amino acid deletions, even outside an epitope will alter protein conformation and change antibody-antigen binding. While the proteins in the claimed composition are known, neither applicant, nor the art have shown which portions of the proteins can be altered while still maintaining the necessary epitopes to induce a bactericidal antibody response. In addition, the written description requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. While claim 4 places no limitations on how much one can alter the proteins in the composition and still consider them to be the same proteins, dependent claims require 85% sequence identity. At 85% sequence identity for each of the proteins, there are more than 1.03×10^{268} possible compositions encompassed by the claims.

When one considers that any amino acid could be changed along the entire protein, the number of proteins encompassed by the claims is far higher than this. When one further considers that there are only $1x10^{78}$ atoms in the entire observable universe (Silk, Excerpt from On the Shores of the Unknown, A Short History of the Universe, Cambridge University Press, see page 10), one of skill in the art would certainly realize that applicant did not have possession of even the tiniest fraction of the claimed genus of proteins.

Regarding argument 3, applicant appears to be addressing a rejection under 35 USC 112, second paragraph. Claim 4 was not rejected for being indefinite. The new designations have no more written description support than what was previously in the claims. Tettelin provided *a* sequence for *a* gene for each of these designations. If applicant is attempting to use these designations to limit the claimed proteins to what was disclosed by Tettelin, there are several problems. First, the dependent claims reciting 85% homology would be broader than the parent claim. Second, Tettelin disclosed nucleic acid sequences, not amino acid sequences. Third, these sequences have not been incorporated by reference. Fourth, this would be essential material which cannot be incorporated by reference to non-patent literature. Fifth, the sequences associated with accession numbers, such as those at Genbank, can be changed, rendering them indefinite. Finally, simply using these designations does not imply that the claims are limited to what was disclosed by Tettelin. Therefore, the designations provide no structural or functional limitations to the claims.

As outlined previously, the rejected claims are drawn to compositions comprising two or more recombinant polypeptides wherein the composition is able to induce a bactericidal antibody response against two or more of hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. Dependent claims limit the composition to where five meningococcal antigens are included: an "NadA" protein, a "NMB1870" protein, a "NMB2091" protein, a "NMB1030" protein, and a "NMB2132" protein. In addition, there are claims drawn which list the "NadA" protein as SEQ ID NO:2, or a protein with 85% identity to SEQ ID NO:2; the "NMB1870" protein as SEQ ID NO:3, or a protein with 85% identity to SEQ ID NO:3; the "NMB2091" protein as SEQ ID NO:4, or a protein with 85% identity to SEQ ID NO:4; the "NMB1030" protein as SEQ ID NO:5, or a protein with 85% identity to SEQ ID NO:5; and the "NMB2132" protein as SEQ ID NO:6, or a protein with 85% identity to SEQ ID NO:6.

The claims are drawn to a vast genus of immunogenic compositions comprising two or more recombinant polypeptides that are capable of inducing a bactericidal antibody response against two or more of hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B (claims 1 and 4), and to compositions with proteins having more than 85% identity with SEQ ID NOs 2, 3, 4, 5, or 6 (claims 5-14). To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that applicant has possession the claimed invention. To adequately describe the genus of immunogenic compositions comprising the claimed composition, applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit the induction of bactericidal antibodies directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*, not just those determinants that would elicit an immune response to the said polypeptides since a given polypeptide can be immunogenic but not induce a bactericidal antibody response directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis.*

The specification discloses a composition comprising an NadA polypeptide with the sequence of SEQ ID NO:2, a fusion protein with the sequence of SEQ ID NO:7 (a fusion of SEQ ID NOs 6 and 5), and a fusion protein with the sequence of SEQ ID NO:8 (a fusion of SEQ ID NO:4 and 3). This composition satisfies the written description requirements. Applicant has not demonstrated that any other composition, including variants of the above composition, is capable of inducing a bactericidal antibody response directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*. The specification further does not disclose distinguishing and identifying features of a representative number of members of the genus of immunogenic compositions to which the claims are drawn, such as a correlation between the structure of the immunoepitope and its recited function (i.e. eliciting the recited immune response), so that the skilled artisan could immediately envision, or recognize at

least a substantial number of members of the claimed genus of immunogenic compositions. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of immunogenic compositions that elicit the induction of bactericidal antibodies directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing

distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan *et al.* (Nature Biotechnology **7**: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of immunogenic compositions that elicit the induction of bactericidal antibodies directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*..

Absent factual evidence, a percentage sequence similarity of less than 100 % is not

deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding utility and/or enablement.

Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus of immunogenic compositions to which the claims refer. Hence, none of the claims meet the written description requirements.

Additionally, claim 4 recites the designations "NadA" protein, "NMB1870" protein, "NMB2091" protein, "NMB1030" protein, and "NMB2132" protein. These terms constitute laboratory designations that do not convey any structural or functional limitations, and which are not described in the specification. Therefore, the proteins to which these designations refer have not been adequately described under the requirements of 35 USC 112, first paragraph. Consequently, only a composition containing the proteins consisting of the sequences of SEQ ID NO:2-6 satisfies the written description requirements of 35 USC 112, first paragraph.

The rejection of claims 4-14 and 26 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the five meningococcal antigens consisting of the sequences of SEQ ID NO:2, 3, 4, 5, and 6, does not reasonably provide enablement for the full breadth of the instant claims, is maintained for the reasons set forth in the previous office action. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues:

1. That the examiner has not provided any reason to doubt that the presently claimed invention is enabled and that the examiner "begins with a discussion of the Wands factors without establishing that an analysis under the Wands factors is appropriate."

2. That the Bowie reference was published in 1990 and therefore has little relevance to the instant application.

3. That the Wells reference teaches that there was a significant degree of predictability sufficient to allow engineering of proteins even in complex areas as of 1990.

4. That Bowie is a discussion of protein structure and function based solely upon sequence homology, which is not relevant to the instant application. Applicant asserts that the relevant characteristic is immunogenicity, which is well-characterized.

5. That Greenspan is not relevant because the claims are not directed to particular epitopes and do not require definition of epitopes for one to make and use the claimed invention. Applicant argues that one of skill in the art can determine which areas of a given protein are conserved and would therefore be less likely to manipulate.

6. That the examiner is basing the enablement on an assertion that epitopes are unpredictable and therefore undue experimentation would be required. Applicant argues that all of the other Wands factors support a determination of enablement. Applicant contends that the application provides guidance by showing sequence alignments of multiple variants, the skill in the art is high, the nature of the invention is simple as any experimentation only requires routine techniques of molecular biology to generate and express mutated variants, and screening for immunogenicity is similarly routine.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.

1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include the "Wands" factors.

Regarding arguments 2 and 3, while Bowie was published in 1990, the teachings therein have not been refuted and have in fact been supported in the intervening years. It is still a well known fact that changing a single amino acid can completely alter protein function, including immunogenicity or antibody binding. In fact, the Wells reference supports this, stating that large deviations from simple additivity can occur when the sites of mutations strongly interact with one another and/or when sites function cooperatively. The important fact to remember when considering Wells is that one may be able to make predictions, but only when one knows the functions of the various motifs within the protein. In the instant case, neither applicant nor the art has provided any guidance to show what portions of the various proteins are necessary to induce a bactericidal antibody response.

Regarding argument 4, applicant's assertion that the relevant characteristic is immunogenicity is incorrect. The claims are not drawn to an immunogenic composition. The claims require a bactericidal antibody response against multiple bacterial strains. This is very different from simple immunogenicity. Since applicant has claimed protein variants that are defined based on sequence homology linked to a function (i.e., inducing a bactericidal antibody response against multiple bacterial strains), a discussion of the link between structure and function based on sequence homology is highly relevant.

Regarding argument 5, as with Bowie, the Greenspan reference is highly relevant. The claimed composition must induce a bactericidal antibody response against particular strains of *Neisseria meningitidis*. As taught in basic immunology texts, an epitope or antigenic determinant interacts with its corresponding antibody based on the three-dimensional structure of both molecules and the fit between them (Cruse *et al.*, Illustrated Dict. of Immunology, 2nd ed., CRC Press, 2003, page 46). These epitopes can be conformational (or discontinuous) epitopes which are formed from separate regions in the primary sequence that are brought together by proper protein folding. Antibodies which bind to conformational epitopes will only bind to proteins folded into their proper native state (Cruse *et al.*, page 166). There are also linear

epitopes, which are regions of six amino acids in the primary sequence of a protein. These are generally not found on the surface of a folded protein and are only available to antibodies upon denaturation of a protein (Cruse *et al.*, page 382). Since the instant claims involve methods of inducing an immune response specific for an organism, not antibodies specific for a particular linear protein, said antibodies must bind to a protein that is in the proper folded state and which is found on the surface of the organism, and therefore must bind to a conformational epitope. Since a conformational epitope is only found in a properly folded protein and can contain discontinuous portions of the protein, there is no way that one could determine whether a given polypeptide would bind to the antibody unless this were empirically tested. Any change (including deletions and substitutions), anywhere along the polypeptide is likely to alter the three-dimensional structure and folding of the protein, thus altering the antibody-antigen interaction. This is further supported by other authors such as McGuinness *et al.* (Mol. Microbiol., 7:505-514, 1993) and Moudallal *et al.* (EMBO Journal, 1:1005-1010, 1982), who have shown that amino acid deletions, even outside an epitope will alter protein conformation and change antibody-antigen binding. Applicant has asserted (backed by the 1990 Wells reference, which does not mention antigen-antibody binding) that the results of changes in the proteins of the invention are predictable. However, Blythe *et al.* (Protein Sci., 14:246-248, 2005) definitively state that one cannot reliably predict the location of epitopes. The sum of the art (both old and new) shows that with regard to generating a particular antibody response, the effects of alterations in the sequence of proteins is entirely unpredictable.

Regarding argument 6, as stated in the previous office action, all of the Wands factors have been considered with regard to the instant claims. However, they will be briefly restated here.

A. Breadth of the claims: The claims are extraordinarily broad. The independent claim places no limit on the number of changes that can be made to each protein. However, several dependent claims limit the proteins to variants with 85% sequence identity. With this level of change, more than $1x10^{268}$ compositions are encompassed. To achieve this number, one must multiply the number of atoms in the observable universe by
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,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000. It is an understatement to say that the claims are broadly drawn.

B. Nature of the invention: The claims are drawn to a combination of proteins that must induce a specific activity in a very complex biological system.

C. State of the prior art: The art clearly shows that one cannot predict the immune response that a given protein will induce unless it has been empirically tested, and any change, even of a single amino acid, can alter this response in an unpredictable way. The art does disclose the sequence of some variants of the proteins in the claimed composition.

D. Level of skill: Applicant has correctly stated the level of skill in the art.

E. Predictability: As stated above, the art shows that the claimed invention is not predictable.

F. Guidance of the specification/Working examples: The specification shows a single example where composition comprising an NadA polypeptide with the sequence of SEQ ID NO:2, a fusion protein with the sequence of SEQ ID NO:7 (a fusion of SEQ ID NOs 6 and 5), and a fusion protein with the sequence of SEQ ID NO:8 (a fusion of SEQ ID NO:4 and 3) is capable of inducing the required immune response. The specification does not disclose any other compositions (or variants of the above composition) that are capable of inducing the required bactericidal antibody response.

G. Quantity of experimentation needed: Given the nature of the claimed invention, it is not enough to simply generate a mutant and test it for immunogenicity. The claimed composition must induce a bactericidal antibody response. This requires the generation of mutants, administration to animals to generate a response, and then further testing to determine whether the response was in fact a bactericidal antibody response. If every single person on the earth were somehow able to test 1 million compositions per hour for 24 hours a day, seven days a week, it would take $1x10^{248}$ years to test the compositions encompassed by the claims.

Therefore, an analysis of the Wands factors shows that it would require undue experimentation to make and use the full scope of the claims.

As outlined previously, enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the

specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to compositions comprising two or more recombinant polypeptides wherein the composition is able to induce a bactericidal antibody response against two or more of hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. Dependent claims limit the composition to where five meningococcal antigens are included: an "NadA" protein, a "NMB1870" protein, a "NMB2091" protein, a "NMB1030" protein, and a "NMB2132" protein. In addition, there are claims drawn which list the "NadA" protein as SEQ ID NO:2, or a protein with 85% identity to SEQ ID NO:2; the "NMB1870" protein as SEQ ID NO:3, or a protein with 85% identity to SEQ ID NO:3; the "NMB2091" protein as SEQ ID NO:4, or a protein with 85% identity to SEQ ID NO:4; the "NMB1030" protein as SEQ ID NO:5, or a protein with 85% identity to SEQ ID NO:5; and the "NMB2132" protein as SEQ ID NO:6, or a protein with 85% identity to SEQ ID NO:6.

Breadth of the claims: The broadest claim encompasses any polypeptides capable of inducing the required immune response in any animal using any means of administration or adjuvant.

Guidance of the specification/The existence of working examples: The specification

discloses a working example wherein a composition comprising an NadA polypeptide with the sequence of SEQ ID NO:2, a fusion protein with the sequence of SEQ ID NO:7 (a fusion of SEQ ID NOs 6 and 5), and a fusion protein with the sequence of SEQ ID NO:8 (a fusion of SEQ ID NO:4 and 3) is capable of inducing the required immune response. However, the specification does not disclose any other compositions (or variants of the above composition) that are capable of inducing the required bactericidal antibody response.

State of the art: While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie *et al.* (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoepitopes**. Bowie *et al.* further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie *et al.* further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan *et al.* (Nature Biotechnology, **7**:936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a particular immune response to a given pathogen can only be identified

empirically. This constitutes undue experimentation.

Consequently, in view of the lack of support in the art and specification, it would require undue experimentation on the part of the skilled artisan to make and use the composition as claimed; therefore, the full scope of the claims is not enabled.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 4-14 and 26 under 35 U.S.C. 103(a) as being unpatentable over Fraser *et al.* (WO 99/57280, 1999) in view of Comanducci *et al.* (J. Exp. Med., 195:1445-1454, 6/2002, IDS filed 4/8/2005), is maintained for the reasons set forth in the previous office action.

Applicant argues:

1. That neither of the cited references teach that any of the polypeptides (either individually or together) would induce an antibody response that is bactericidal against two or more of hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. Applicant states that the examiner has incorrectly asserted that Comanducci teaches that allele 3 of NadA has such function and Guiliani teaches that NadA by itself does not produce bactericidal antibodies against at least one lineage 3 strain. Applicant argues that because neither of the references teach all of the elements of the claimed invention, there is no *prima facie* case for obviousness.

2. That the examiner has engaged in hindsight reconstruction. Fraser discloses more than 1500 polypeptides and there are $7x10^{15}$ combinations of these. Applicant asserts that the examiner has not provided a reason that one would select the claimed combination from the numerous possible combinations. Applicant argues that, while the examiner makes the proposition that it is obvious to combine two compositions which are taught to be useful for the

same purpose, neither Fraser nor Comanducci teach the utility of the disclosed polypeptides to provide the claimed bactericidal activity.

3. That the claimed invention "produces a surprising result which is a secondary consideration sufficient to rebut any *prima facie* case of obviousness." Applicant refers to Giuliani *et al.* which discloses "results obtained with the presently claimed five antigens in a vaccine composition."

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, first, contrary to applicant's assertion, the examiner has not claimed that Comanducci teaches that allele 3 of NadA has this function. The examiner stated "Comanducci *et al.* disclose a composition comprising NadA, which induces bactericidal antibodies against two or more of hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B." Whether Comanducci recognized it or not, NadA induces bactericidal antibodies against two or more of hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. This is shown by the instant application. The fact that Giuliani has shown that NadA does not induce the claimed activity in lineage 3 strains has no relevance since the claims require activity of the entire composition (not just NadA) against *two or more* of hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. Despite the fact that this activity is only required of the entire composition, NadA by itself *does* induce this activity. Furthermore, there is no need for the references to teach that the combination of polypeptides would induce a bactericidal antibody response, as this is an inherent characteristic of these polypeptides. A composition containing polypeptides with the sequences of SEQ ID NOs 2-6 would have this effect, regardless of whether or not one recognized it.

Regarding argument 2, Fraser is one of several references that disclose these polypeptides. Applicant has acknowledged, both in the specification and in their arguments, that the polypeptides are known. The question is whether one would have had a reason to combine them. Applicant argues that, because Fraser and Comanducci do not teach that the proteins provide the claimed bactericidal activity, there is no reason to combine the proteins. However, there is no need for one to have the same motivation as applicant. Each of the proteins is taught to be individually useful as a vaccine against *N. meningitidis* serogroup B. Therefore, combining them in a vaccine against *N. meningitidis* serogroup B is obvious. Furthermore, as stated by the

Supreme Court in *KSR International Co. v. Teleflex Inc.*, No. 04-1350 (U.S. Apr. 30, 2007), it is obvious to combine elements when all of the claimed elements (i.e. polypeptides of SEQ ID NOs 2-6) are known in the prior art and one skilled in the art could have combined them by known methods with no change in their respective function, yielding nothing more than predictable results.

Regarding argument 3, applicant's assertion that a surprising result "is a secondary consideration sufficient to rebut any *prima facie* case of obviousness" is incorrect. In fact, the ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The submission of objective evidence of patentability does not mandate a conclusion of patentability in and of itself. *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987). Although the record may establish evidence of secondary considerations which are indicia of nonobviousness, the record may also establish such a strong case of obviousness that the objective evidence of nonobviousness is not sufficient to outweigh the evidence of obviousness. *Newell Cos. v. Kenney Mfg. Co.,* 864 F.2d 757, 769, 9 USPQ2d 1417, 1427 (Fed. Cir. 1988), *cert. denied*, 493 U.S. 814 (1989); *Richardson-Vicks, Inc., v. The Upjohn Co.*, 122 F.3d 1476, 1484, 44 USPQ2d 1181, 1187 (Fed. Cir. 1997) (showing of unexpected results and commercial success of claimed ibuprofen and pseudoephedrine combination in single tablet form, while supported by substantial evidence, held not to overcome strong *prima facie* case of obviousness). In addition, applicant has not shown unexpected results commensurate in scope with the claims. First, the Giuliani reference does not use the claimed invention. Giuliani used a vaccine comprising fusion proteins rather than separate proteins (it is noted that applicant chose not to elect fusion proteins in their response to the restriction requirement). Second, based on what applicant refers to as "art-recognized designations" used in the claims and in the Giuliani reference, Giuliani did not even use the same antigens as the claimed invention. Third, the claims encompass any variant of the claimed proteins, while Giuliani shows the effects of a single combination of proteins. Considering the broad scope of the instant claims, Giuliani's results are hardly commensurate. Finally, unexpected results must be unexpected. There is nothing unexpected about antigens generating an immune response against strains that they are known to generate an immune

response against. If one combines vaccines that are individually effective against different strains, one would expect to get a multivalent vaccine that is effective against those different strains; the idea of a multivalent vaccine is not novel.

As outlined previously, the instant claims are drawn to compositions comprising two or more recombinant polypeptides wherein the composition is able to induce a bactericidal antibody response against two or more of hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B (claim 1). Dependent claims limit the composition to where five meningococcal antigens are included: an "NadA" protein, a "NMB1870" protein, a "NMB2091" protein, a "NMB1030" protein, and a "NMB2132" protein (claim 4); wherein the NadA protein is SEQ ID NO:2 (claim 6), or a protein with 85% identity to SEQ ID NO:2 (claim 5); wherein the "NMB1870" protein is SEQ ID NO:3 (claim 8), or a protein with 85% identity to SEQ ID NO:3 (claim 7); wherein the "NMB2091" protein is SEQ ID NO:4 (claim 10), or a protein with 85% identity to SEQ ID NO:4 (claim 9); wherein the "NMB1030" protein is SEQ ID NO:5 (claim 12), or a protein with 85% identity to SEQ ID NO:5 (claim 11); and wherein the "NMB2132" protein is SEQ ID NO:6 (claim 14), or a protein with 85% identity to SEQ ID NO:6 (claim 13), further comprising a pharmaceutically acceptable carrier (claim 26).

Fraser *et al.* disclose vaccines that contain *Neisseria meningitidis* polypeptides (see page 34, final section). Said polypeptides can be prepared recombinantly (see page 6, paragraph 3) and the vaccines contain an effective amount of immunogenic polypeptides (see page 36, paragraph 2). Among the proteins listed to be used in said vaccines are NadA (see SEQ ID NO:2944, page 1377), a "741" protein comprising SEQ ID NO:3 (see SEQ ID NO:2536, page 1205), a "936" protein comprising SEQ ID NO:4 (see SEQ ID NO:2884, page 1352), a "953" protein comprising SEQ ID NO:5 (see SEQ ID NO:2918, page 1365), and a "287" protein comprising SEQ ID NO:6 (see SEQ ID NO:1202, page 671).

Fraser *et al.* differs from the instant invention in that, while vaccines containing multiple antigens are disclosed, they do not specifically disclose that the vaccines should contain an "NadA" protein, a "741" protein, a "936" protein, "a 953" protein, and a "287" protein. Furthermore, the NadA protein disclosed does not have the sequence of SEQ ID NO:2.

Comanducci *et al.* disclose a composition comprising NadA, which induces bactericidal antibodies against two or more of hypervirulent lineages A4, ET-5, and lineage 3 of *N.*

meningitidis serogroup B (see abstract). Said NadA protein has the sequence of the instant SEQ ID NO:2 (see figure 4, allele 3).

According to MPEP 2144.06, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Therefore, it would have been obvious to use the "NadA" protein, "741" protein, "936" protein, "953" protein, and "287" protein in a vaccine composition against *N. meningitidis* serogroup B because these proteins are taught to be individually useful for that purpose.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian J Gangle/
Examiner, Art Unit 1645

/Shanon A. Foley/
Supervisory Patent Examiner, Art Unit 1645